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The role of neutrophil to lymphocyte ratio as a predictor of left ventricular diastolic dysfunction in chronic kidney disease patients

Znaczenie stosunku liczby neutrofili do limfocytów jako czynnika predykcyjnego dysfunkcji rozkurczowej lewej komory serca u chorych z przewlekłą chorobą nerek

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Abstract

Introduction. Left ventricular diastolic dysfunction (LVDD) occurs very often in patients with chronic kidney disease (CKD). The neutrophil to lymphocyte ratio (NLR) is a novel inflammatory marker, which has a predictive value in different cardiovascular diseases. We have evaluated the association between NLR and LVDD among CKD patients.

Material and methods. The study group consisted of 54 ambulatory patients with CKD at stages 3–5 with preserved left ventricular (LV) systolic function. The CKD patients were divided into two groups, depending on the results of mitral early diastolic velocity EmLV: the group with LV diastolic dysfunction LVDD(+), when EmLV < 8 cm/s, and the group with normal LV diastolic function LVDD(–), when EmLV ≥ 8 cm/s. NLR was calculated as the ratio of the neutrophil and lymphocyte counts.

Results. Patients in LVDD(+) group had significantly higher values of NLR when compared to patients in LVDD(–) group (2.51 [1.12–9.82] vs. 1.75 [0.99–3.64], p = 0.007). NLR negatively correlated with EmLV (r = –0.311, p = 0.021), while positively with N-terminal B-type natriuretic propeptide (r = 0.292, p = 0.037). Among the examined parameters, NLR was an independent predictive factor for LVDD with odds ratio 3.14 (95% confidence interval [CI] 1.05–9.42), p = 0.034. The area under the receiver operating characteristics curve for NLR was 0.714 (95% CI 0.575–0.828), p = 0.003, and using a cut point of 1.77, the NLR predicted LVDD with a sensitivity of 92.3% and specificity of 53.6%.

Conclusions. This study suggests that elevated neutrophil to lymphocyte ratio as an indicator of inflammation seems to be a useful marker of LVDD in CKD patients.

Key words: neutrophil to lymphocyte ratio, diastolic dysfunction, chronic kidney disease

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Introduction

Chronic kidney disease (CKD) is a major public health problem, affecting 10–15% of the adult general population. Cardiovascular diseases are the most common cause of mortality in patients with CKD [1, 2]. Heart failure with preserved ejection fraction (HFpEF), characterised by normal left ventricular ejection fraction and abnormalities of ventricular filling, including decreased diastolic distensibility and impaired relaxation is independently associated with morbidity and mortality in CKD patients [3–5]. Left ventricular hypertrophy due to arterial hypertension and chronic anaemia, either calcium phosphate disturbances or hypervolemia are important factors for developing left ventricular diastolic dysfunction (LVDD) in this patients' population [6, 7]. The previous studies have shown that persistent inflammation, which occurs in CKD, may lead to development of LVDD [8]. In recent years, neutrophil to lymphocyte ratio (NLR) was proposed as a novel marker to determine inflammation in cardiac and non-cardiac disorders and it (is readily available in the routine blood analysis. Although the relationship between NLR and almost all cardiovascular diseases have been investigated, the importance of NLR in diastolic dysfunction in CKD patients remains unclear. In our study, we have evaluated the association between NLR and LVDD among CKD patients.

Material and methods

The study group consisted of 54 ambulatory patients with CKD at stages 3–5, with preserved left ventricular (LV) systolic function defined at echocardiography by an LV ejection fraction (LVEF) > 50%, with lack of regional wall motion abnormalities and with sinus rhythm. The exclusion criteria comprised as follows: LV systolic dysfunction, previous myocardial infarction, cardiomyopathy, significant valvular heart diseases, cancer, active chronic inflammation or acute infectious diseases within four weeks.

Echocardiography

The echocardiographic evaluations of all the subjects were performed by a single, experienced cardiologist who was not informed of the clinical or laboratory findings of the patients. Standard echocardiography was performed in all the patients using a GE 6S device with 2.5–3.5 MHz transducer. M-mode echocardiography and a quantitative analysis were conducted using parasternal long axis images based on data provided by the American Society of Echocardiography [9]. The left ventricular end-diastolic dimension (LVEDD), right ventricular end-diastolic dimension (RVEDD), left atrial dimension (LAD), interventricular septal diastolic diameter (IVSd), left ventricular posterior wall dimension at diastole (LVPWd), were obtained using M-mode echocardiographic tracings under the guide of 2D imaging. The left ventricular ejection fraction (LVEF) was calculated according to the biplane modified Simpson's method. Left ventricular mass (LVM) was calculated with the formula recommended by the American Society of Echocardiography (ASE), modified by Devereux [10]. The obtained results of LVM were indexed by the body surface area of the patient and presented as the left ventricular mass index (LVMI). The mitral inflow early diastolic wave (E), late diastolic wave (A), E/A ratio, deceleration time (DT) of the E wave, were measured on pulsed wave Doppler echocardiography in a four chamber view [9].

Tissue Doppler echocardiography examination

Using pulsed wave tissue Doppler echocardiography, systolic and diastolic velocities were measured by placing the Doppler gate on the lateral mitral annulus at the posterior leaflet of the mitral valve. The following parameters were measured: mitral annular systolic velocity (SmLV), early diastolic velocity (EmLV), and late diastolic velocity (AmLV) of the lateral part of the examined annulus [11]. The ratio of early transmitral velocity (E) to the mitral annular early diastolic velocity (EmLV) was used as an approximation of mean left atrial pressure (E/EmLV). All the parameters were calculated as the mean of measurements taken in three consecutive cardiac cycles. Diastolic dysfunction of left ventricular was defined as EmLV < 8 cm/s [12].

The CKD patients were divided into two groups depending on the results of EmLV: LVDD(+) group with LV diastolic dysfunction when EmLV < 8 cm/s, and LVDD(–) group with normal LV diastolic function, when EmLV ≥ 8 cm/s.

Biochemical tests

Blood samples of all the individuals were collected on the day of echocardiographic examination and the following laboratory parameters were measured for all the patients: serum creatinine concentration, estimated glomerular filtration rate (eGFR) evaluated by the modified MDRD (Modification of diet in Renal Disease) formula, as well as the serum levels of urea, phosphorus (P), calcium (Ca), C-reactive protein (CRP), parathormone (PTH) and N-terminal B-type natriuretic propeptide (NT-proBNP) levels were calculated by immunoassay with the Stratus® CS Acute Care™ Siemens.

Additionally, blood samples were taken and the following parameters were recorded: red cell distribution width (RDW), mean corpuscular volume (MCV), haemoglobin concentration (Hb), platelets (PLT), mean platelet volume (MPV), neutrophils and lymphocytes count. NLR was calculated as the ratio of the neutrophil and lymphocyte counts. The platelet-to-lymphocyte ratio (PLR) was calculated as the platelet count divided by the lymphocyte count.

Statistical analysis

The values of parameters with normal distribution were presented as a mean ± standard deviation, whereas values with non-normal distributions were expressed as a median

and range. Normal distribution of continuous variables was tested using Kolmogorov-Smirnov's and Shapiro-Wilk's tests. Continuous variables with normal distribution were compared using Student's *t*-test and those without normal distribution were compared using Mann-Whitney's U test. The chi-square test was used to compare the categorical variables. The correlation analyses were made using Spearman's test. The receiver operating characteristic (ROC) analysis curves served to determine the optimal cut-off points of the NLR in association with LV diastolic dysfunction.

The multivariate logistic regression analysis was performed to assess the independent predictors of LV diastolic dysfunction and the results were shown as odds ratio (OR) with 95% confidence intervals (95% CI). A value of $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using Statistica 6 software and MedCalc (version 12.5.0).

All the patients consented in writing for the inclusion in the research. The study protocol was approved by the bioethics committee.

Results

Clinical and echocardiographic characteristics

The present study included 54 patients (25 males and 29 females aged 67.9 ± 12) with CKD at stages 3–5. The patients were divided into two groups depending on the results of EmLV: LVDD(+) group with LV diastolic dysfunction when EmLV < 8 cm/s, and LVDD(–) group with normal LV diastolic function, when EmLV ≥ 8 cm/s. Distribution of the baseline characteristics and echocardiographic data obtained by statistical analyses among the groups is summarised in Table 1. The mean age was 68.7 ± 12.2 in the group of 26 CKD patients with LVDD while it was 67.1 ± 12.3 in the group of 28 CKD patients without LVDD ($p = 0.636$). The patients of both groups did not differ in gender, presence of arterial hypertension and diabetes. There was no statistically significant difference between two groups by the means of body mass index (BMI). Patients with LVDD, as compared to patients without LVDD, were characterised by more advanced stage of CKD (Table 1).

In echocardiography, patients with LVDD(+), as compared to patients with LVDD(–)were characterised by significantly higher values of LVMI, IVSd, LVPWd, DT, E/EmLV ratios, and lower values of E, EmLV, E/A ratios and Em/AmLV ratios. No differences were noted for the following parameters: LVEDD, RVEDD, LAD, LVEF, LVFS, A, SmLV and AmLV.

Laboratory data

Patients with LVDD, as compared to patients without LVDD, were characterised by significantly lower serum Ca levels and higher CRP levels, whereas serum of creatinine, urea, P and NT-proBNP were of borderline significance. There was no statistically significant difference between two groups in serum of parathormone levels.

Patients with LVDD had significantly higher NLR values when compared to the group of patients without LVDD (2.51 [1.12–9.82) vs. 1.75 [0.99–3.64], $p = 0.007$). Other parameters of blood count analysis were also evaluated and are presented in Table 2. RDW-SD, MCV, Hb, PLT, MPV, neutrophil and the mean value of platelet to lymphocyte ratio (PRL) did not differ significantly between two groups, only lymphocyte value was lower in LVDD(+) group compared with LVDD(–) group.

Spearman's correlation analyses showed that NLR was negatively correlated with echocardiographic parameters of diastolic dysfunction, EmLV ($r = -0.311$, $p = 0.021$) and positively correlated with NT-proBNP ($r = 0.292$, $p = 0.037$) and parathormone ($r = 0.284$, $p = 0.038$).

In order to determine independent parameters indicating LV diastolic dysfunction in CKD patients, univariate and multivariate logistic regression analyses were performed. Into multivariable analysis, only parameters with $p < 0.1$ in univariate logistic regression were included. Among the examined parameters, the NLR was found to be an independent predictive factor for LV diastolic dysfunction, except BMI and Ca (Table 3).

In the receiver operating characteristics (ROC) curve analysis, a level of NLR > 1.77 predicted LV diastolic dysfunction in CKD patients with 92.3% sensitivity and 53.6% specificity. The area under the ROC curve for NLR was 0.714 (95% CI 0.575–0.828, $p = 0.003$) (Figure 1).

Discussion

In our study, we have found that NLR level was increased in CKD patients with LV diastolic dysfunction compared with CKD patients without diastolic dysfunction, and was an independent predictive factor for LV diastolic dysfunction with OR 3.14, 95% CI 1.05–9.42, $p = 0.034$. Furthermore, the NLR showed negative correlation with EmLV, and positive correlation with NT-proBNP and PTH plasma levels. Moreover, using a cut point of 1.77, the NLR predicted LV diastolic dysfunction with a sensitivity of 92.3% and specificity of 53.6%.

Numerous studies have demonstrated that an increased neutrophil count might reflect an inflammation and that lymphopenia is an indicator of physiologic stress, which may lead to the cortisol secretion. The NLR have been associated with poor outcomes in patients with cardiovascular disease. However, the NLR has proved to predict mortality more accurately than other absolute neutrophil or lymphocyte counts [13, 14]. To the best of our knowledge, this study is the first research which showed the importance of NLR levels in detection of diastolic dysfunction among patients with CKD.

Table 1. Baseline characteristics, biochemical and echocardiographic findings of both groups

Parameter	LVDD(+) group (n = 26)	LVDD(–) group (n = 28)	p
Age	68.7 ± 12.2	67.1 ± 12.3	0.636
Gender [M/F]	15/11	10/18	0.111
BMI [kg/m^2]	28.1	30.8	0.072
Hypertension, n [%]	21 (81)	23 (82)	0.896
Stage 3 CKD, n [%]	12 (46)	24 (85)	0.002
Stage 4 CKD, n [%]	10 (38)	3 (11)	0.017
Stage 5 CKD, n [%]	4 (15)	1 (4)	0.134
Diabetes, n [%]	5 (19)	7 (25)	0.610
Creatinine [mg/dL]	2.1 (1.2–6.3)	1.5 (1.0–4.3)	0.055
eGFR [mL/min/1.73 m^2]	30.1 ± 14.5	37.2 ± 12.6	0.059
Urea [mg/dL]	75 (30–160)	59 (20–137)	0.057
P [mg/dL]	3.8 (2.7–7.8)	3.5 (2.3–5.9)	0.062
Ca [mg/dL]	8.7 ± 0.8	9.3 ± 0.8	0.019
CRP [mg/mL]	4.1 (1.0–36)	3.0 (1.0–30)	0.045
Log PTH [pg/mL]	1.99 ± 0.32	1.88 ± 0.31	0.193
Log NT-proBNP [pg/mL]	2.52 ± 0.47	2.28 ± 0.39	0.053
LVEDD [cm]	4.8 ± 0.6	4.6 ± 0.4	0.131
RVEDD [cm]	2.8 ± 0.2	2.7 ± 0.2	0.185
LAD [cm]	4.3 ± 0.5	4.0 ± 0.5	0.125
IVSd [cm]	1.2 (1.0–1.5)	1.1 (0.9–1.5)	0.010
LVPWd [cm]	1.2 (0.9–1.4)	1.1 (0.9–1.5)	0.034
LVEF [%]	58.1 ± 5.4	59.9 ± 5.5	0.218
LVMI [g/m^2]	106.5 (60.2–198)	89.0 (57.9–137.5)	0.006
LVFS [%]	30.1 ± 4.1	31.0 ± 3.4	0.365
E [cm/s]	55 ± 15	72 ± 19	0.001
A [cm/s]	80 (55–141)	74 (50–118)	0.585
DT [ms]	250 ± 58	221 ± 44	0.043
E/A ratio	0.62 (0.42–1.24)	0.9 (0.56–1.9)	< 0.001
SmLV [cm/s]	7 (5–14)	8 (5–11)	0.096
EmLV [cm/s]	6 (3–7)	9 (8–14)	< 0.001
AmLV [cm/s]	10.4 ± 2.4	9.8 ± 2.6	0.383
EmLV/AmLV ratio	0.54 (0.35–1.0)	0.95 (0.56–2.25)	< 0.001
E/EmLV ratio	9.5 ± 2.2	7.8 ± 2.3	0.009
NLR	2.51 (1.12–9.82)	1.75 (0.99–3.64)	0.007

LVDD(+) – group with left ventricular diastolic dysfunction; LVDD(–) – group without left ventricular diastolic dysfunction; M – male; F – female; BMI – body mass index; CKD – chronic kidney disease; eGFR – estimated glomerular filtration rate; P – serum levels of phosphorus; Ca – serum levels of calcium; CRP – C-reactive protein; log PTH – logarithm of parathormone; log NT-proBNP – logarithm of N-terminal pro-brain natriuretic peptide; LVEDD – left ventricular end-diastolic dimension; RVEDD – right ventricular end-diastolic dimension; LAD – left atrial diastolic dimension; IVSd – interventricular septal diastolic diameter; LVPWd – left ventricular posterior wall dimension at diastole; LVEF – left ventricular ejection fraction; LVMI – left ventricular mass index; LVFS – left ventricular fractional shortening; E – early transmitral velocity; A – late transmitral velocity; DT – deceleration time; E/A ratio – ratio of early transmitral velocity to late transmitral velocity; SmLV – mitral annular systolic velocity; EmLV – mitral annular early diastolic velocity; AmLV – mitral annular late diastolic velocity; EmLV/AmLV – ratio of mitral annular early diastolic velocity to mitral annular late diastolic velocity; E/EmLV ratio – ratio of early transmitral velocity to mitral annular early diastolic velocity; NLR – neutrophil to lymphocyte ratio

The previous studies have reported that the NLR has emerged as a new marker in different diseases, including cardiac disorders. The prognostic value of NLR has demonstrated in pulmonary embolism, coronary artery disease, myocardial infarction, stroke, and heart failure (HF) [15–19]. Beyond atherosclerotic disorders, NLR was also found to be associated with idiopathic dilated cardiomyopathy, mitral annular calcification, infective endocar-

Table 2. Evaluation of other haematological parameters

Parameter	LVDD(+) group (n = 26)	LVDD(–) group (n = 28)	p
RDW-SD [%]	14.1 (12.9–19.5)	13.7 (12.7–16.2)	0.104
MCV	89.9 ± 4.8	89.6 ± 4.5	0.823
Hb	12.4 ± 1.5	12.4 ± 1.8	0.901
PLT	198 (89–484)	213 (126–453)	0.446
MPV	11.1 ± 1.1	11.1 ± 0.9	0.975
Neutrophil	4.07 ± 0.92	3.94 ± 1.21	0.666
Lymphocyte	1.62 ± 0.55	2.14 ± 0.78	0.007
PLR	122 (64–322)	109 (61–242)	0.077
NLR	2.51 (1.12–9.82)	1.75 (0.99–3.64)	0.007

LVDD(+) — group with left ventricular diastolic dysfunction; LVDD (–) — group without left ventricular diastolic dysfunction; RDW-SD — red cell distribution width-standard deviation; MCV — mean corpuscular volume; Hb — haemoglobin concentration; PLT — platelets; MPV — mean platelet volume; PLR — platelet to lymphocyte ratio; NLR — neutrophil to lymphocyte ratio

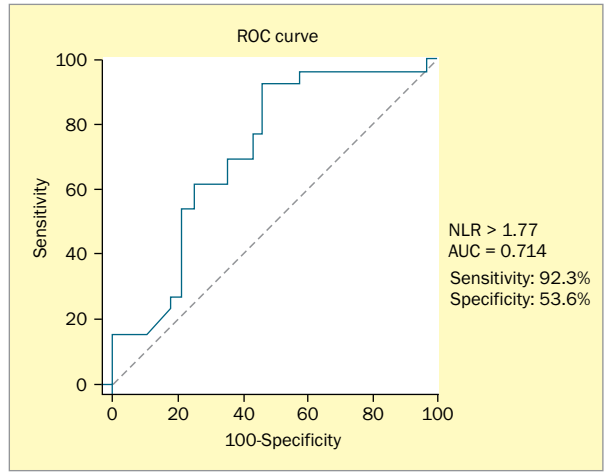

Figure 1. The receiver operating characteristic curves for neutrophil to lymphocyte ratio (NLR) to predict left ventricle diastolic dysfunction; ROC — receiver operating characteristics; AUC — area under curve

Table 3. Biochemical parameters for the prediction of left ventricle diastolic dysfunction (EmLV < 8 cm/s). Univariate and multivariate logistic regression analysis

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Creatinine [mg/dL]	2.02	1.04–3.95	0.033	1.27	0.26–6.26	0.760
Urea [mg/dL]	1.02	1.00–1.04	0.035	1.02	0.97–1.06	0.388
Ca [mg/dL]	0.41	0.18–0.92	0.028	0.30	0.10–0.89	0.025
Log NT-proBNP [pg/mL]	3.70	0.91–14.99	0.059	0.65	0.08–4.88	0.674
BMI [kg/m^2]	0.90	0.81–1.01	0.078	0.80	0.67–0.96	0.016
NLR	2.39	1.13–5.04	0.018	3.15	1.05–9.42	0.035

CI — confidence interval; Ca — serum levels of calcium; BMI — body mass index; Log NT-proBNP — logarithm of N-terminal B-type natriuretic propeptide; NLR — neutrophil to lymphocyte ratio; OR — odds ratio

ditis and atrial septal aneurysm [20–23]. Moreover, other studies have found that NLR was increased in non-dippers with arterial hypertension when compared with dipper and normotensive subjects. Additionally, NLR significantly correlated with blood pressure variation rate, and itwas found to be an independent predictor of blood pressure variability [24]. It is widely suggested that inflammation plays an important role in the progression and severity of cardiac diseases. The functional and structural impairment of heart and development of cardiovascular diseases may be associated with increased levels of inflammatory markers, which shows the balance between degenerative and controlled inflammatory responses. Inflammatory processes play a pivotal role in the development of HF and CKD [25, 26]. White blood cells and their subtypes release many inflammatory cytokines, such as tumour necrosis factor α (TNF-α), interleukin 6 (IL-6), and CRP as a result of inflammatory stimulus. These pro-inflammatory cytokines have destructive effect on the myocardium, resulting in decreased LV function and occur heart failure [27, 28]. This situation may happenin the developing HFpEF, where the crucial role is played by the diastolic dysfunction of the left ventricle. The previous studies have shown that higher levels of pro-inflammatory cytokines may lead to myocardial remodelling [29]. Karagöz A et al. [30] presented that hypertension patients with diastolic dysfunction had higher values of NLR compared to subjects without diastolic dysfunction. Moreover, when grades of diastolic dysfunction were evaluated, patients with third grade of diastolic dysfunction had the highest NLR values, while patients with first grade had the lowest, supporting an association between diastolic dysfunction and NLR in hypertension patients [30]. In our study, we have showed that CKD patients with LV diastolic dysfunction had significantly higher NLR value compared with CKD patients without LV diastolic dysfunction. Furthermore, the NLR

was an independent predictive factor for LV diastolic dysfunction in this population. In our research, CRP level was higher in group with diastolic dysfunction compared with group without diastolic dysfunction. Interestingly, CRP level did not reach statistical significance in univariate logistic regression analysis for the diagnosis of LV diastolic dysfunction in CKD patients. Additionally, PLR did not differ between both groups. In summary, among our inflammatory parameters, the best predictive value indicating LV diastolic dysfunction in patients with CKD was NLR only. We know, that patients with LVDD had more advanced CKD than patients without diastolic dysfunction (46% patients were in third stage and 54% in fourth and fifth stages of CKD in LVDD group compared to group without LVDD, where were 85% in third stage and only 15% in fourth and fifth stages). However, the serum creatinine concentration in both groups was not statistically significant, but only of borderline significance. We believe, that our study may inspire further trials to investigate the mechanism involved in the development of LV diastolic dysfunction in CKD patients and evaluate the possible role of inflammation in this process.

Study limitations

The present study has several limitations. It was a single-centre study, based on a small number of patients, so it is unclear whether the results can be applied to other populations. Our analyses are based on single measurements of blood test marker. In addition, we could not study the other inflammatory markers, such as fibrinogen, TNF-α, and interleukins. The presence of diabetes mellitus should be an exclusion criterion, however as the amount of diabetes in both groups was similar, it was decided not to exclude them from the study, but it obviously limited our study.

Conclusion

This study showed, that NLR seems to be a useful marker of LVDD in CKD patients. NLR may be used as an additional, simple, reliable and economic marker of LV diastolic dysfunction. Further prospective studies, with larger sample sizes are needed to shed the light on the mechanism underlying this association.

Acknowledgement

The authors of this manuscript declare that they have complied with the Principles of Ethical Publishing present in the Declaration of Helsinki, and that the study protocol was approved by the local ethics committee. There are no financial or other relationship considerations that could lead to any conflict of interest.

Streszczenie

Wstęp. Dysfunkcja rozkurczowa lewej komory serca (LVDD) często rozwija się u osób z przewlekłą chorobą nerek (CKD). Stosunek liczby neutrofilów do liczby limfocytów (NLR) jest nowym markerem zapalnym, który uznaje się także za czynnik predykcyjny wielu chorób układu sercowo-naczyniowego. W opisanym badaniu oceniano związek między NLR a LVDD wśród chorych na CKD.

Materiał i metody. Do badania włączono 54 chorych w 3.–5. stadium CKD z zachowaną frakcją wyrzutową lewej komory. Pacjentów podzielono na dwie grupy zależnie od wartości prędkości wczesnej fazy rozkurczowej pierścienia mitralnego (EmLV) — grupę z dysfunkcją rozkurczową lewej komory LVDD(+), kiedy EmLV wynosi poniżej 8 cm/s i grupę z prawidłową funkcją rozkurczową lewej komory LVDD(–), kiedy EmLV wynosi 8 cm/s lub więcej.

Wyniki. Pacjenci z grupy LVDD(+) charakteryzowali się istotnie wyższymi wartościami NLR niż chorzy z grupy LVDD(–), odpowiednio (2,51 [1,12–9,82] *v.* 1,75 [0,99–3,64]; p = 0,007). Stosunek liczby neutrofilów do liczby limfocytów korelował ujemnie z EmLV (r = –0,311; p = 0,021) oraz dodatnio ze stężeniem N-końcowego fragmentu propetydu natriuretycznego typu B (r = 0,292, p = 0,037). Spośród badanych parametrów NLR było niezależnym czynnikiem predykcyjnym LVDD z ilorazem szans 3,14 (95-proc. przedział ufności [CI] 1,05–9,42); p = 0,034. Pole powierzchni pod krzywą (ROC) dla NLR w rozpoznaniu LVDD wynosiło 0,714 (95% CI 0,575–0,828; p = 0,003), a wartość NLR 1,77 uzyskana w analizie ROC charakteryzowała się 92,3-procentową czułością i 53,6-procentową swoistością w rozpoznaniu LVDD.

Wnioski. Wyniki badania sugerują, że podwyższony NLR jako parametr stanu zapalnego może być użytecznym markerem LVDD u chorych na CKD.

Słowa kluczowe: stosunek neutrofilów do limfocytów, dysfunkcja rozkurczowa, przewlekła choroba nerek

Folia Cardiologica 2018; 13, 1: 1–8

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